

FOURIER

sub analysis diabetes

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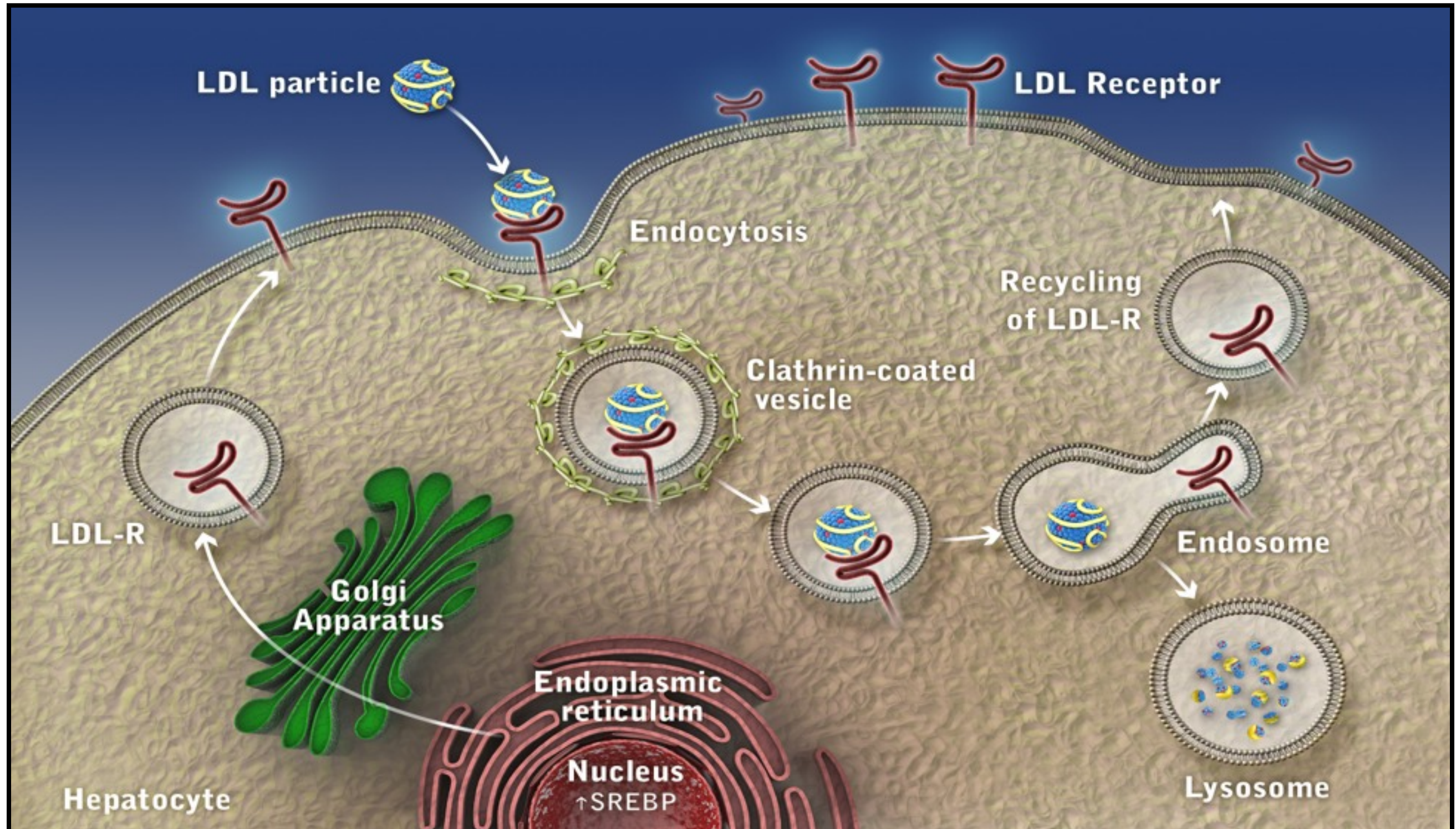
Disclosure

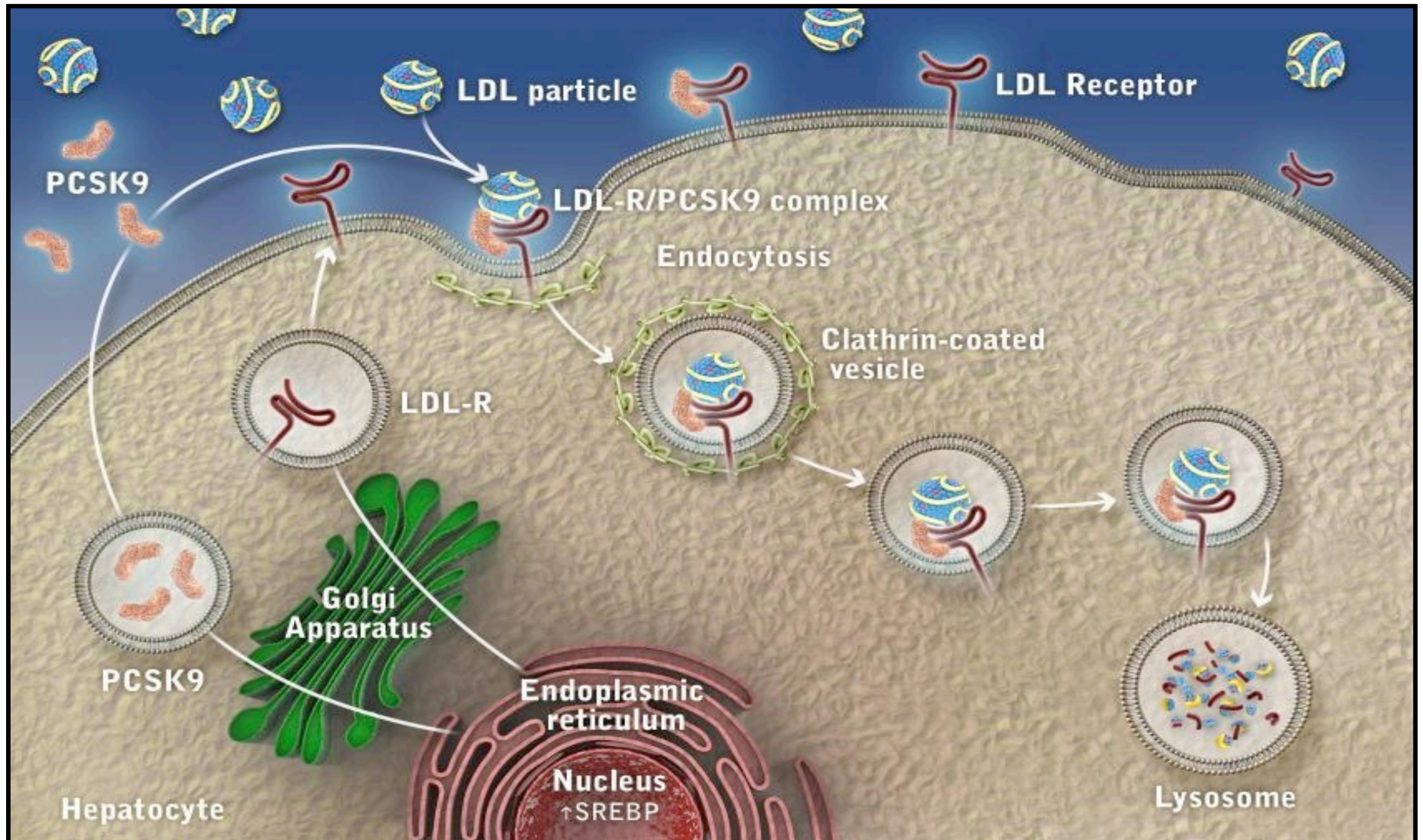
- Consultant and/or speaker for pharmaceutical companies that develop molecules that influence lipoprotein metabolism, including Regeneron, Pfizer, MSD, Sanofi, Amgen
 - PI for clinical trials in dyslipidemia conducted with (a.o.) Amgen, Sanofi, Eli Lilly, Novartis, Kowa, Genzyme, Cerenis, Pfizer, Dezima, Astra Zeneca
- Research grants: ZonMW, EU, Amgen, Sanofi, AstraZeneca Aegerion, Synageva

The department and/or Vascular Research Foundation receives the honoraria and investigator fees.

No shares or Stock, No ownership

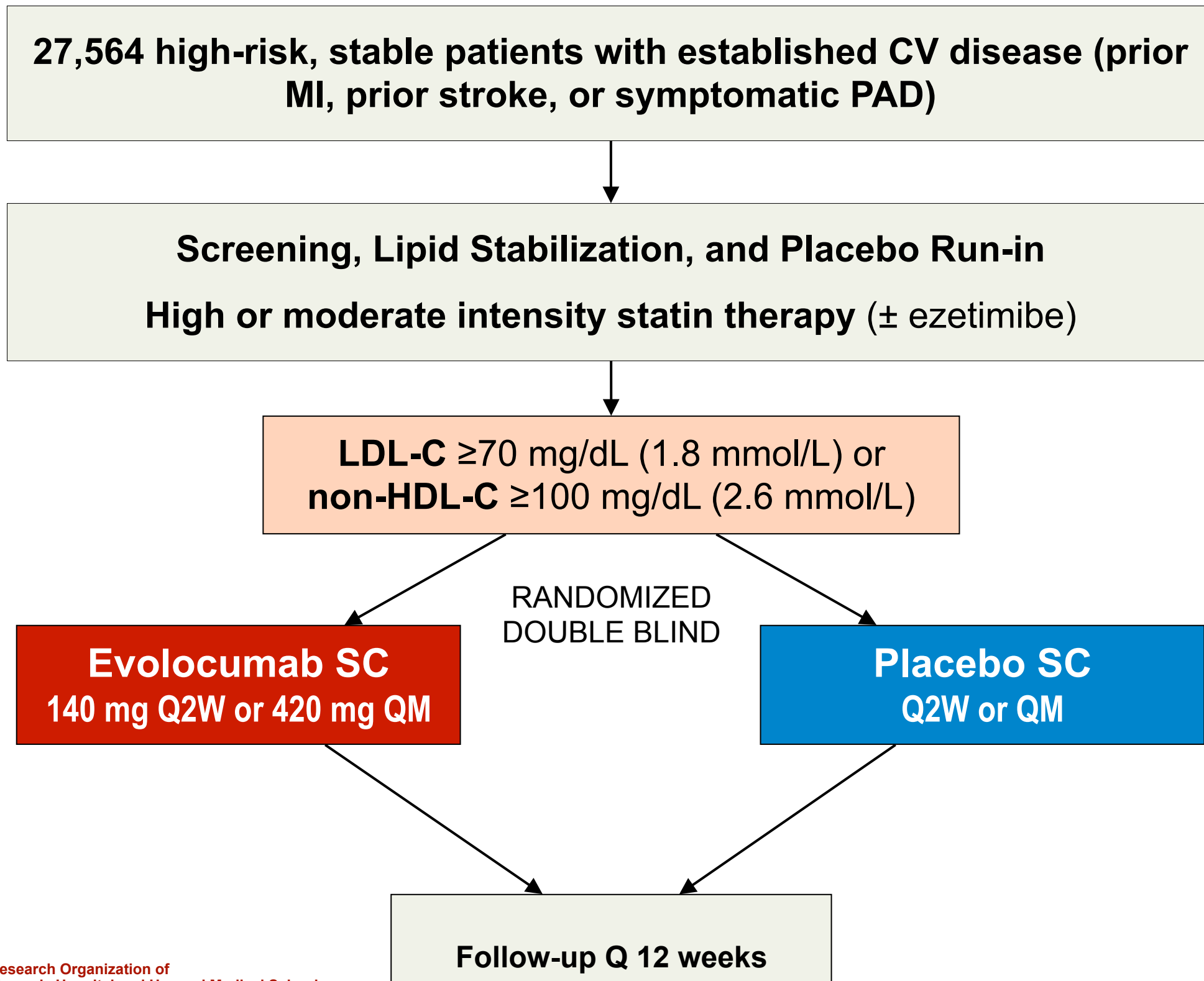
LDL receptor mediated cholesterol uptake







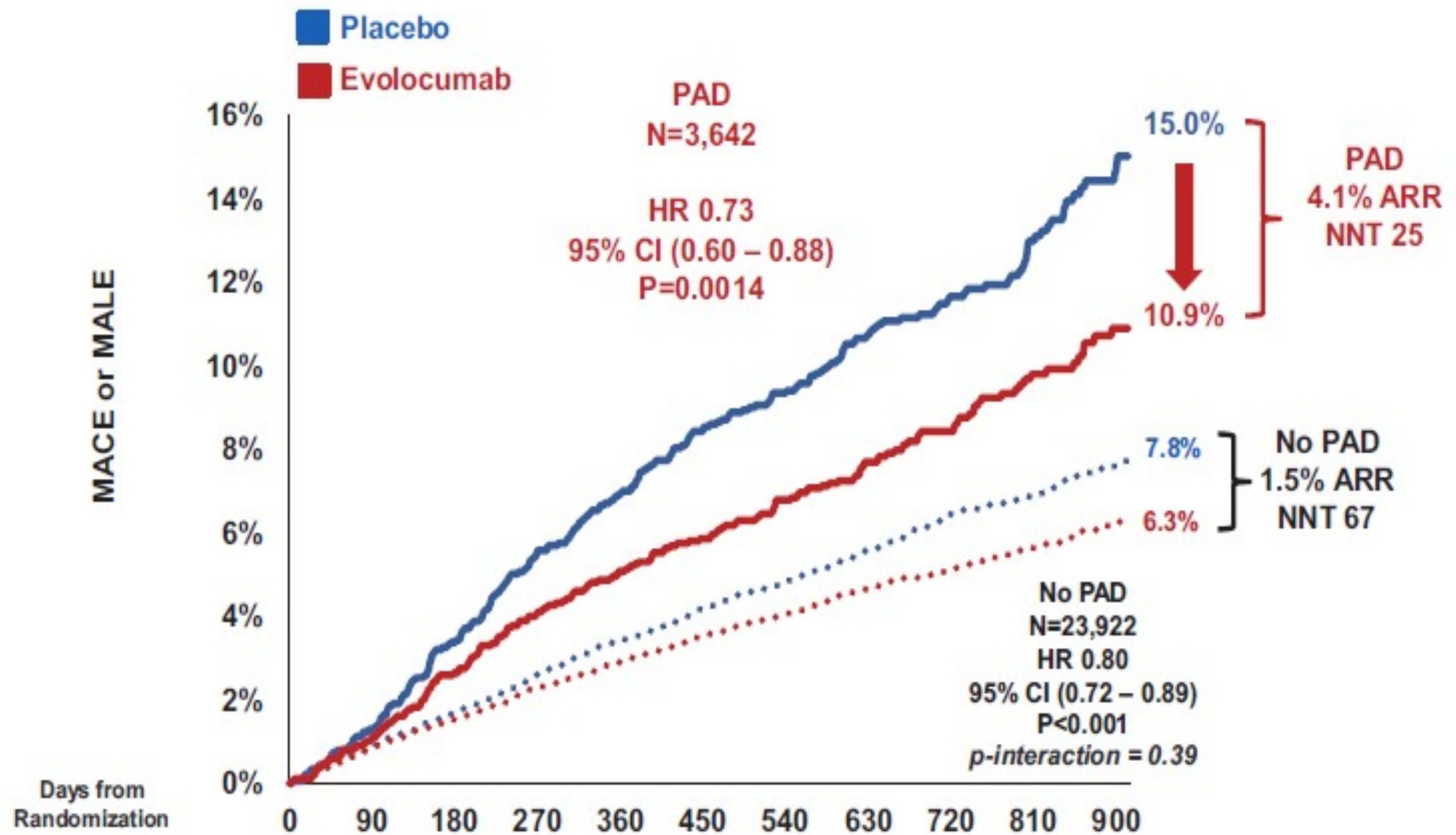
Trial Design



	N	Cumulative incidence of CV death, MI, or stroke	ARR	NNT
Overall patients with prior MI	N= 22,351	--	--	--
Time from Qualifying MI	< 2 y ago N=8,402	10.8%	2.9%	35
	≥ 2 y ago N=13,918	9.3%	1.0%	101
Number of Prior MIs	≥ 2 N=5,285	15.0%	2.6%	38
	1 N=17,047	8.2%	1.7%	60
Residual Multivessel CAD	MVD N=5,618	12.6%	3.4%	29
	No MVD N=16,715	8.9%	1.3%	78

Marc Sabatine AHA Anaheim 2017

MACE or MALE in Patients with and without PAD



Number at risk

Placebo PAD	1784	1753	1711	1665	1630	1601	1555	1305	994	712	438
Evolocumab PAD	1858	1832	1798	1764	1741	1721	1671	1412	1078	765	471
Placebo no PAD	11996	11859	11727	11600	11486	11367	10758	9089	7160	5424	3630
Evolocumab no PAD	11926	11802	11698	11582	11488	11394	10825	9133	7254	5471	3647

Two questions:

- *Do PCSK9 inhibitors induce DM?*
- *How do patients with DM respond to PCSK9 antibody therapy?*

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LDL-R/HMGCR and Diabetes

NOD:

Lines of Evidence

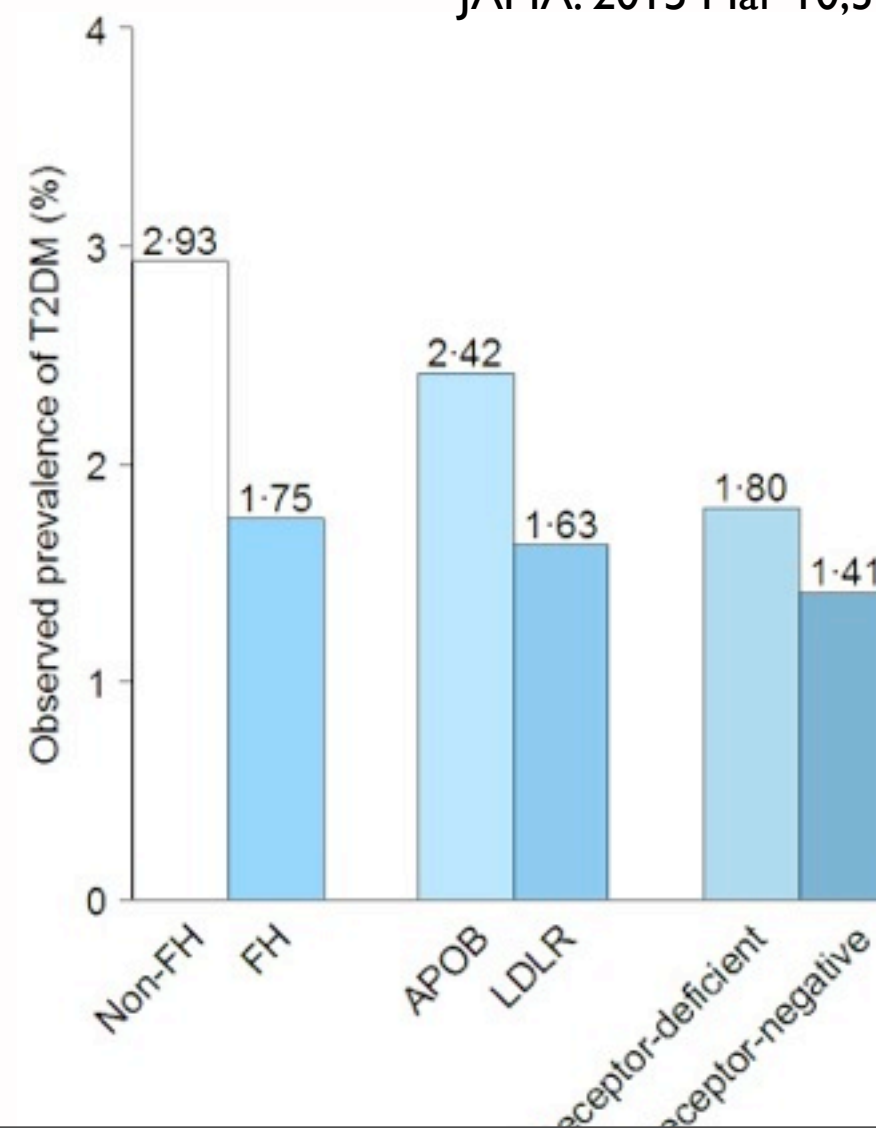
- 1) statin trials (JUPITER)
- 2) GWAS
- 3) extreme genetics

Original Investigation

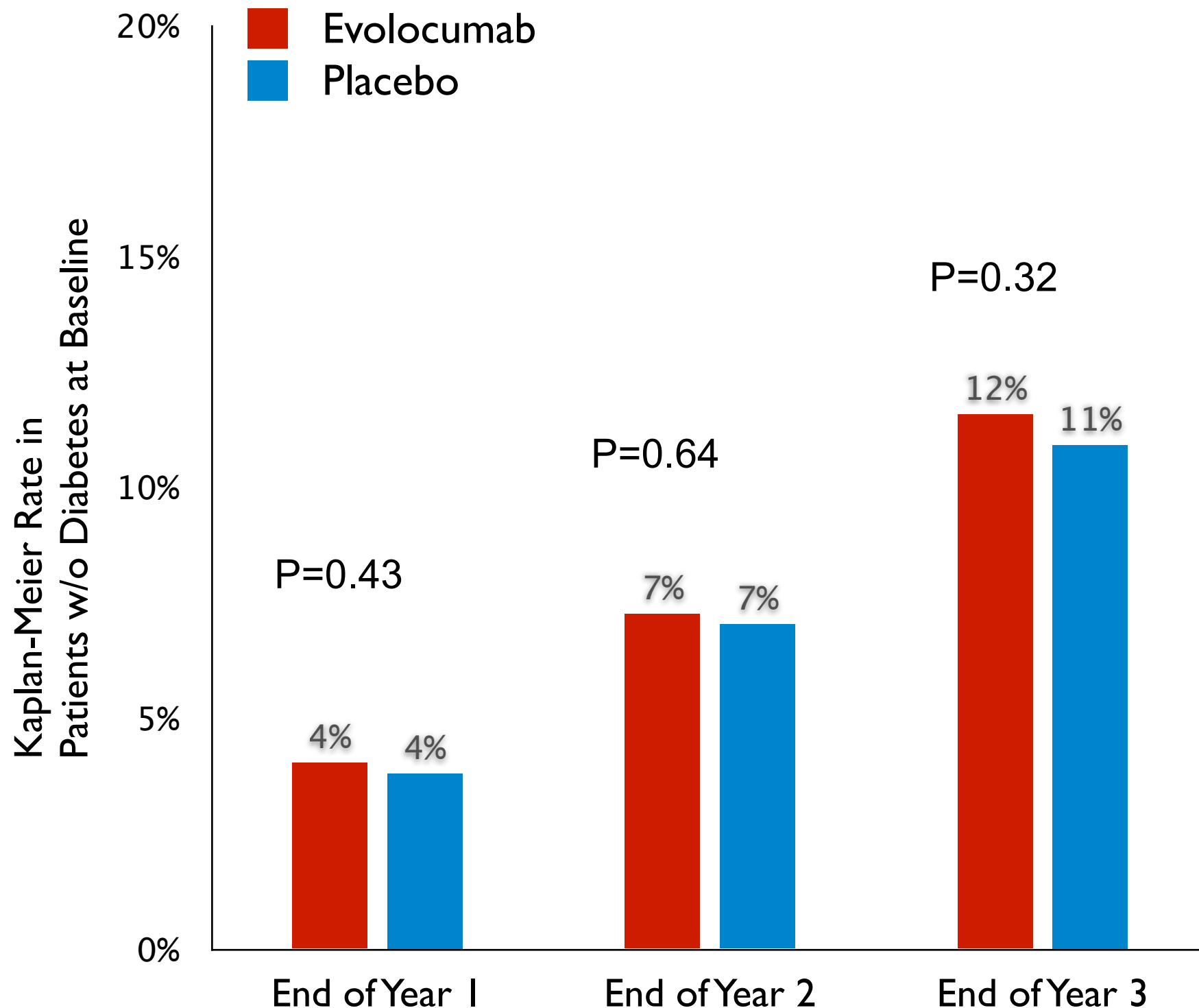
Association Between Familial Hypercholesterolemia and Prevalence of Type 2 Diabetes Mellitus

Joost Besseling, MD; John J. P. Kastelein, MD, PhD; Joep C. Defesche, PhD;
Barbara A. Hutten, PhD, MSc; G. Kees Hovingh, MD, PhD

JAMA. 2015 Mar 10;313(10):1029-36



New-Onset Diabetes



In all patients w/o diabetes at baseline (1294 incident cases in 16,510 patients):

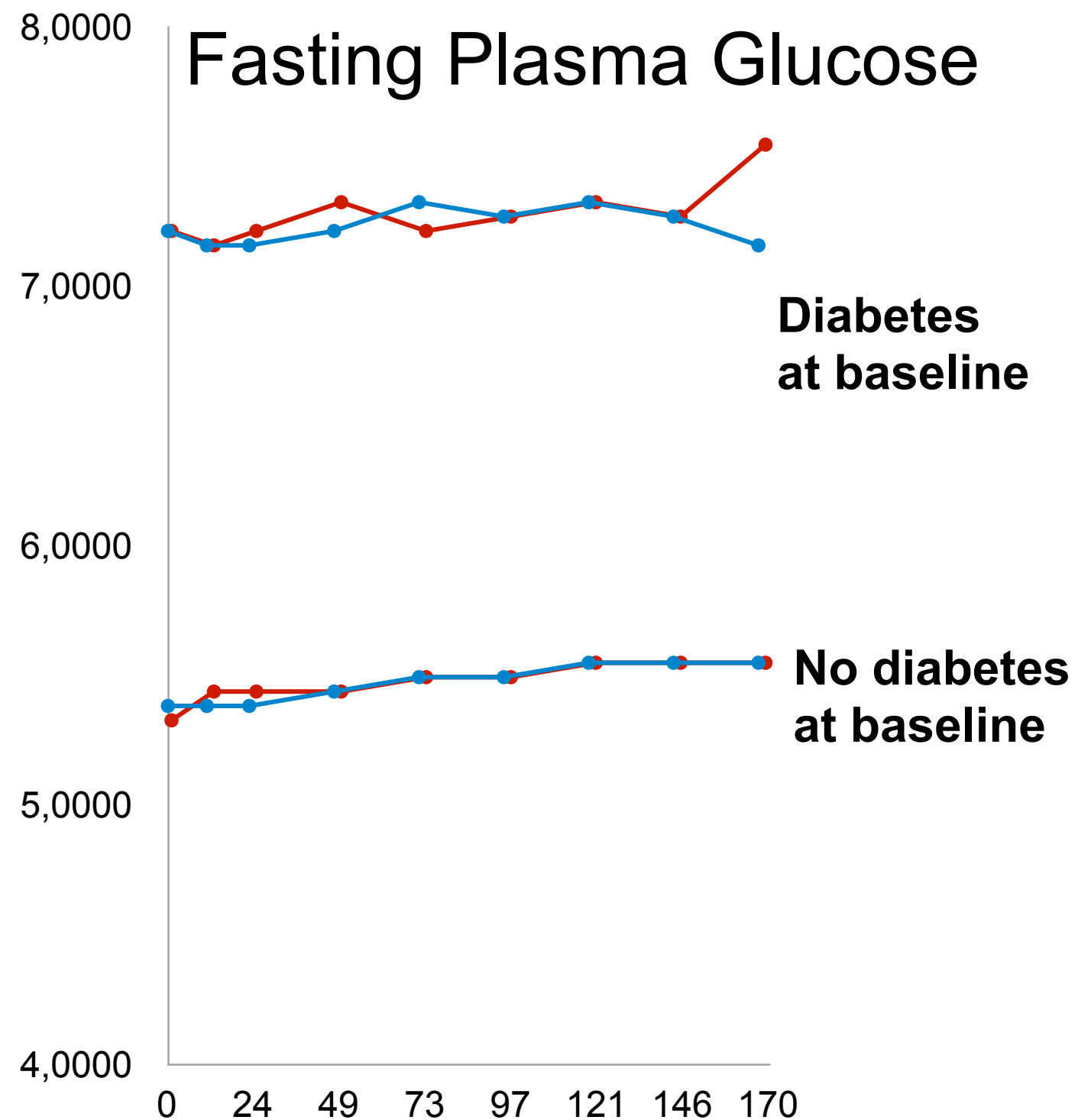
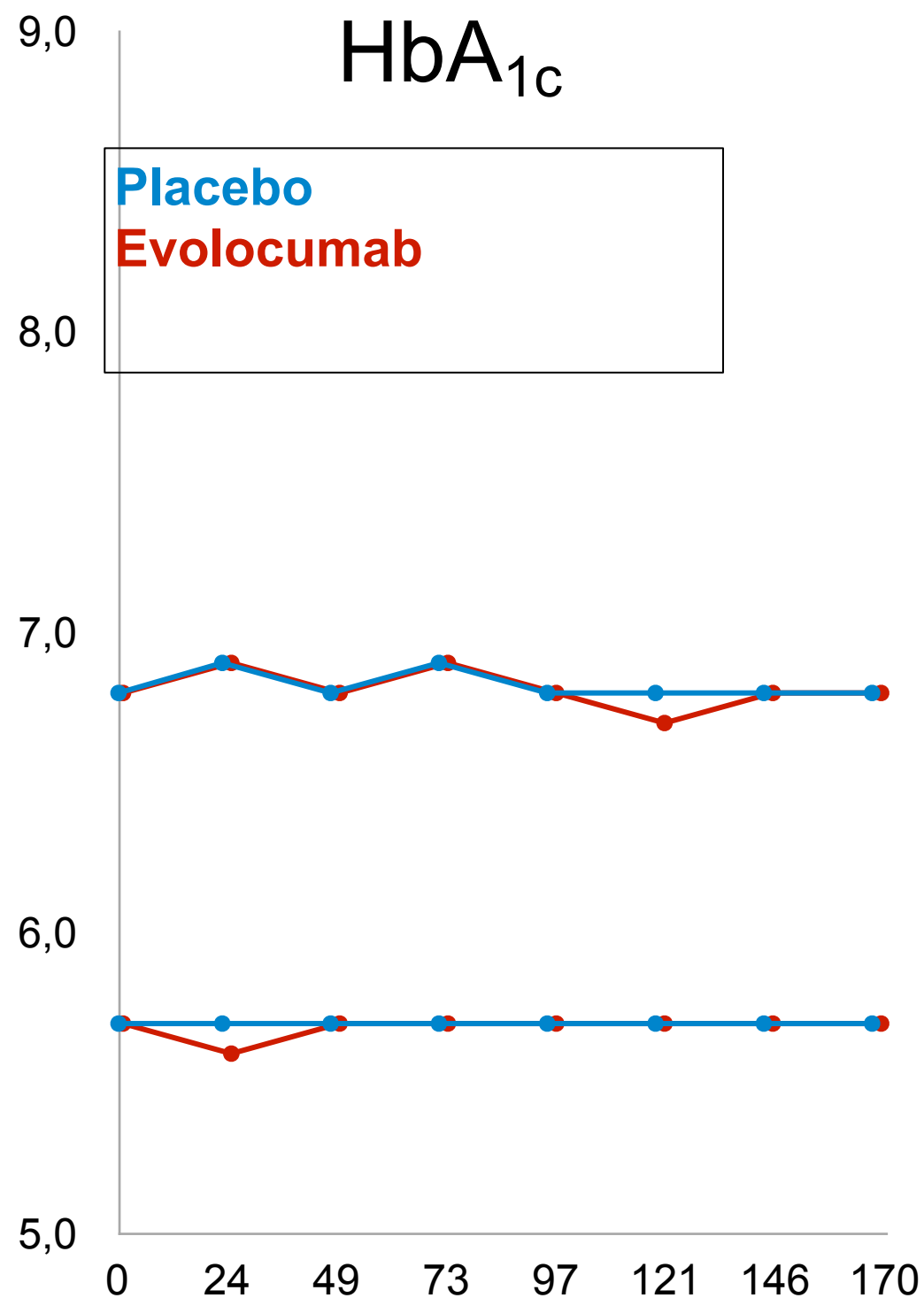
HR 1.05 (95% CI 0.94-1.17)

In patients w/ prediabetes at baseline (1163 incident cases in 10,338 patients):

HR 1.00 (95% CI 0.89-1.13)

- Sabatine MS. Presented at the European Association for the Study of Diabetes 53rd annual meeting, Lisbon, September 2017

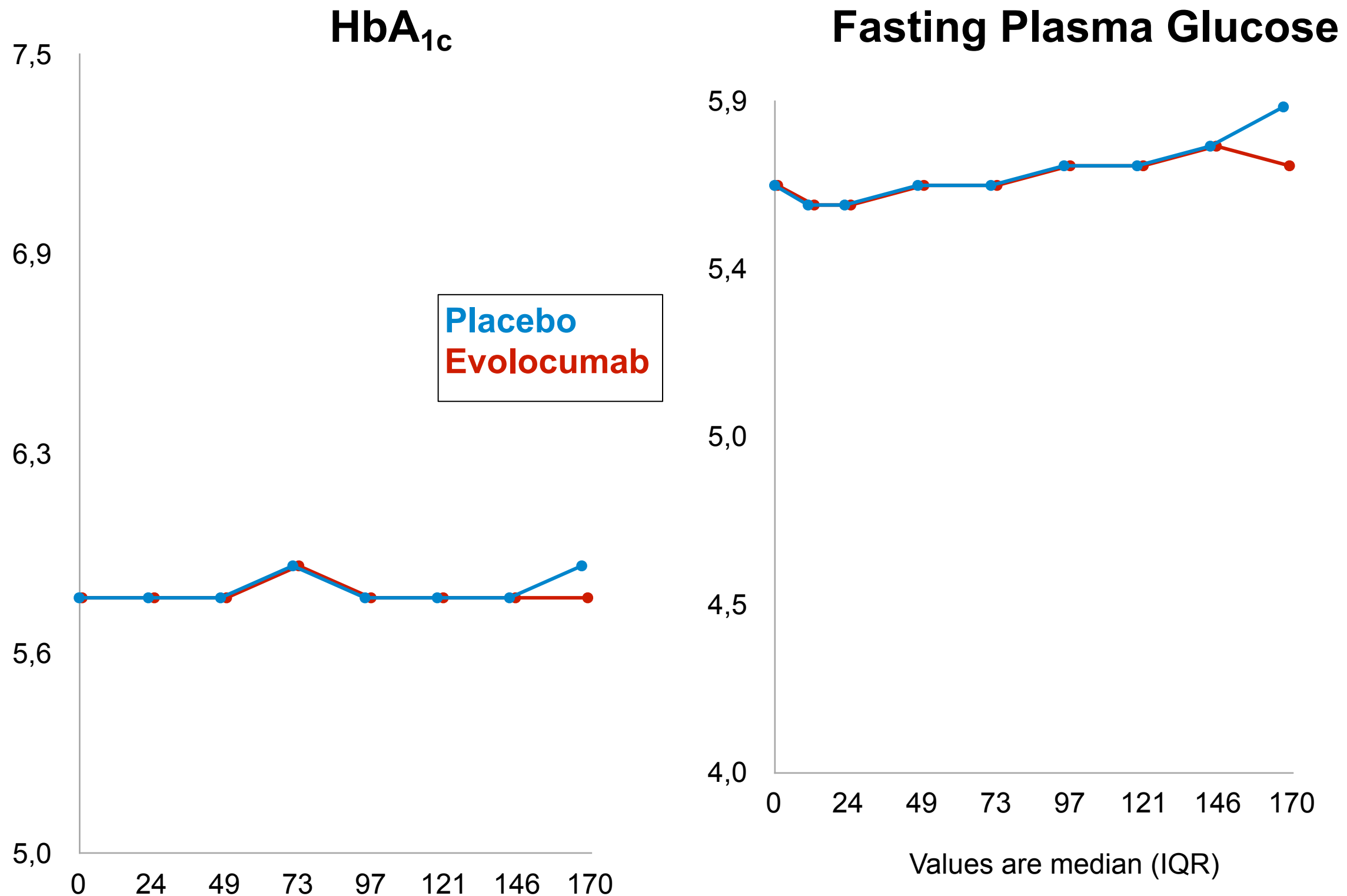
Glycemic Parameters



Values are median (IQR)

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Glycemic Parameters in Prediabetes



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Change in bodyweight



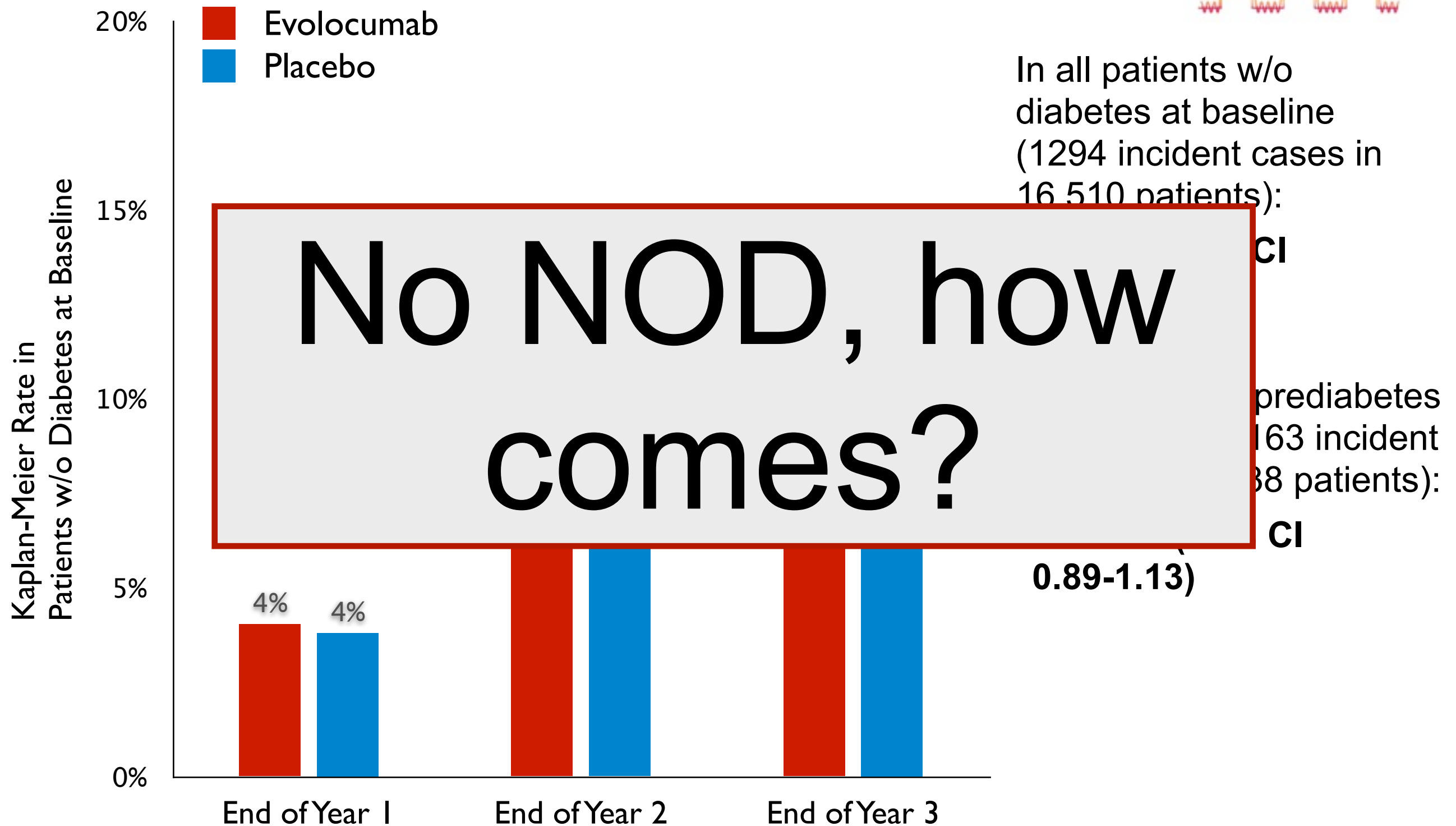
Subgroup	Evolocumab	Placebo
Patients with diabetes	-0.1 (-2.1, 1.6)	-0.1 (-2.0, 1.7)
Patients without diabetes	0.3 (-1.3, 2.0)	0.3 (-1.3, 2.0)
Patients with prediabetes	0.2 (-1.4, 2.0)	0.3 (-1.4, 2.0)
Patients with normoglycemia	0.3 (-1.3, 2.0)	0.3 (-1.3, 2.0)

Bodyweight in kg. Values are median (IQR) of time-weighted average for post-baseline measurements.

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New-Onset Diabetes

fourier



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Fourier and NOD strengths and limitations

- Largest trial of PCSK9i
- ~3× # of events (CV and new-onset diabetes) than prior studies
- CV events and new-onset DM adjudicated
- Serial glycemia measurements
- Median trial duration 2.2 years
- All patients on background statin therapy
- No glucose tolerance testing



Jeffrey Hamilton/Getty



Anti-PCSK9 antibodies — beneficial or inducers of diabetes?

Rutger Verbeek and G. Kees Hovingh

A recent study has shown that evolocumab, an injectable monoclonal antibody directed against proprotein convertase subtilisin/kexin type 9 (PCSK9), robustly reduces levels of LDL cholesterol and decreases the risk of cardiovascular disease in patients with and without diabetes mellitus. When given on top of statins, evolocumab does not induce diabetes mellitus.

Refers to Sabatine, M. S. et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. Lancet Diabetes Endocrinol. [http://dx.doi.org/10.1016/S2213-8587\(17\)30313-3](http://dx.doi.org/10.1016/S2213-8587(17)30313-3) (2017)

Effect of the Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor Evolocumab on Glycemia, Body Weight, and New-Onset Diabetes Mellitus.

Sattar N¹, Toth PP², Blom DJ³, Koren MJ⁴, Soran H⁵, Uhart M⁶, Elliott M⁷, Cyrille M⁶, Somaratne R⁶, Preiss D⁸.

Odyssey Outcomes

Event	Alirocumab (N=9451)	Placebo (N=9443)
Diabetes worsening or diabetic complications: <i>pts w/DM at baseline</i> , n/N (%)	506/2688 (18.8)	583/2747 (21.2)
New onset diabetes; <i>pts w/o DM at baseline</i> , n/N (%)	648/6763 (9.6)	676/6696 (10.1)
General allergic reaction, n (%)	748 (7.9)	726 (7.8)
Hepatic disorder, n (%)	500 (5.3)	534 (5.7)
Local injection site reaction, n (%)*	360 (3.8)	203 (2.1)
Neurocognitive disorder, n (%)	143 (1.5)	167 (1.8)
Cataracts, n (%)	120 (1.3)	134 (1.4)
Hemorrhagic stroke, n (%)	9 (<0.1)	16 (0.2)

R vs. placebo 1.82 (95% CI 1.54, 2.17)



Two questions:

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- *How do patients with DM respond to PCSK9 antibody therapy?*

FOURIER diabetes substudy

- Baseline Diabetes Subgroups
 - **Diabetes**: either clinical history per patient; CEC review of baseline medical records; or baseline HbA1c $\geq 6.5\%$ or FPG ≥ 126 mg/dL (7.0 mmol/L)
 - **No diabetes**
 - *Prediabetes*: baseline HbA1c 5.7-6.4% or FPG 100-125 mg/dL (5.5-6.9 mmol/L)
 - *Normoglycemia*: none of the above
- Outcomes
 - **Primary endpoint**: CV death, MI, stroke, hospitalization for UA, coronary revasc
 - **Key secondary endpoint**: CV death, MI, stroke
 - **Adverse events in general**; new-onset diabetes; glycemia
- TIMI Clinical Events Committee (CEC)
 - **Adjudicated all efficacy endpoints & new-onset diabetes (per ADA definitions)**
 - **Members unaware of treatment assignment & lipid levels**

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FOURIER diabetes substudy

Characteristic	Diabetes (N=11,031)	No Diabetes (N=16,533)
Age, years, mean (SD)	63 (9)	62 (9)
Female sex (%)	27	23
White race (%)	80	88
Weight, kg, mean (SD)	88 (19)	83 (16)
Type of cardiovascular disease (%)		
Myocardial infarction	79	83
Stroke (non-hemorrhagic)	22	18
Symptomatic PAD	15	12
Cardiovascular risk factor (%)		
Hypertension	87	75
Current cigarette use	22	32
eGFR, mL/min per 1.73 m ² (SD)	75 (21)	76 (17)

All P values <0.0001 apart from age (P=0.55)

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FOURIER diabetes substudy

Characteristic	Diabetes (N=11,031)	No Diabetes (N=16,533)
Statin use (%)		
High-intensity	67	71
Moderate-intensity	33	29
Ezetimibe use (%)	4	6
Median lipid measures, mmol/L (IQR)		
LDL-C	2.3 (2.0-2.8)	2.4 (2.1-2.8)
Total cholesterol	4.3 (3.9-4.8)	4.4 (3.9-4.9)
HDL-C	1.1 (0.9-1.3)	1.2 (1.0-1.4)
Triglycerides	1.7 (1.3-2.3)	1.4 (1.1-1.9)

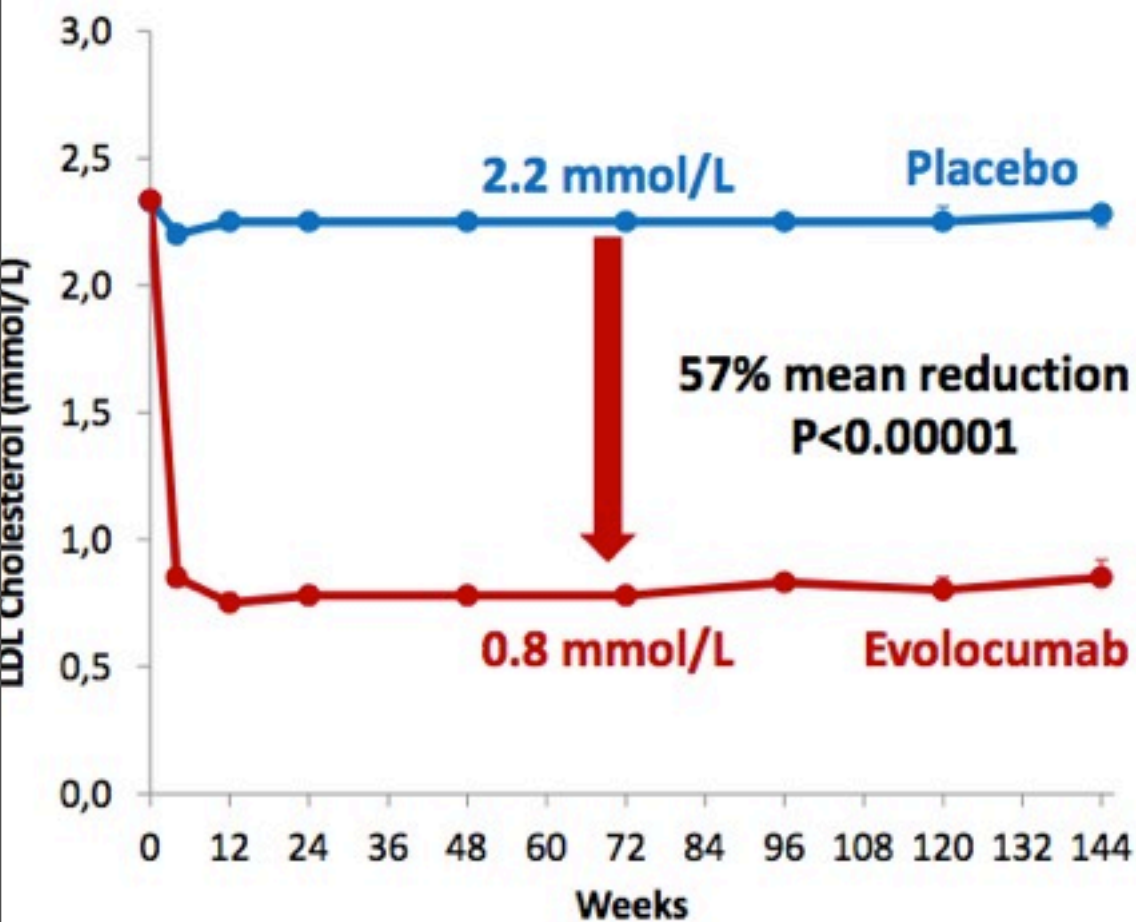
Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines. All P values <0.0001

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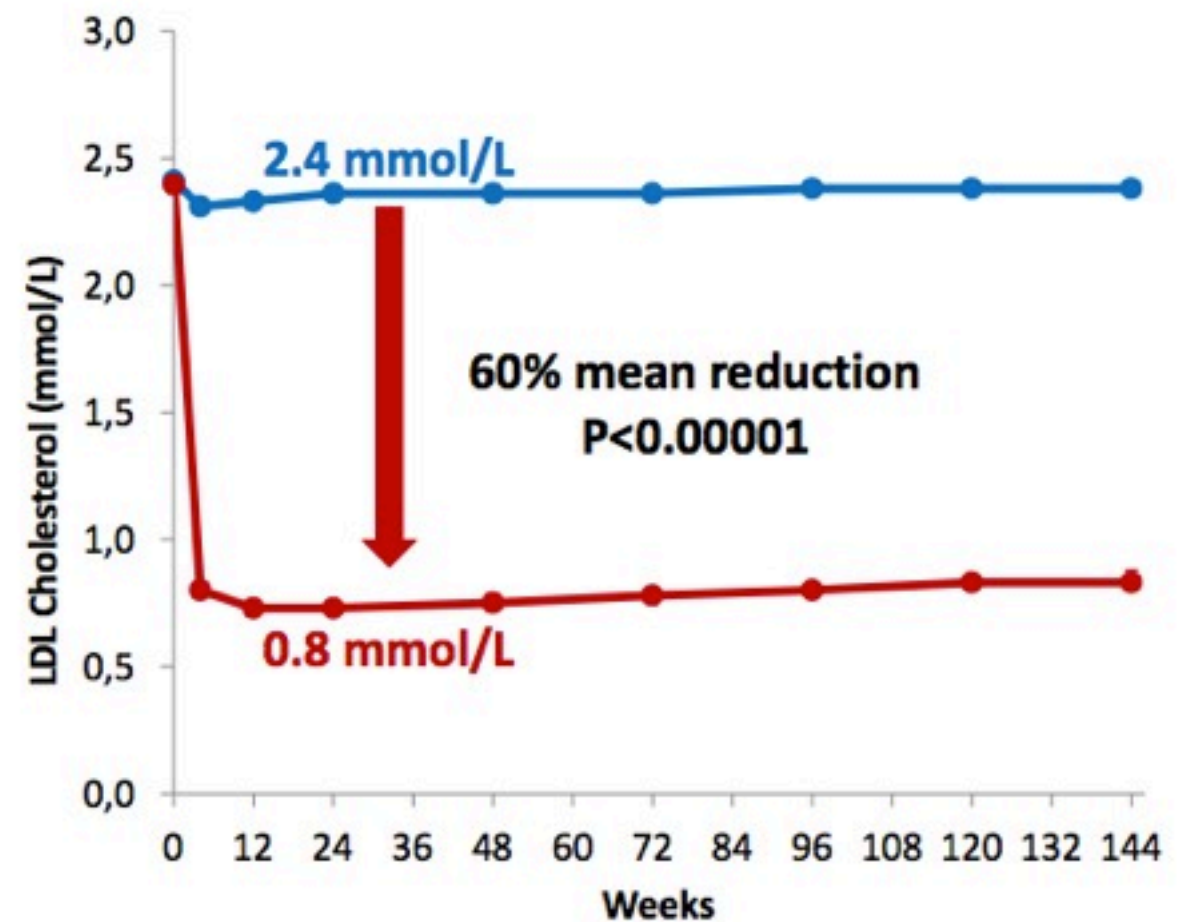
FOURIER diabetes substudy

effect of evolocumab on LDL-C

Patients w/ Diabetes at Baseline



Patients w/o Diabetes at Baseline



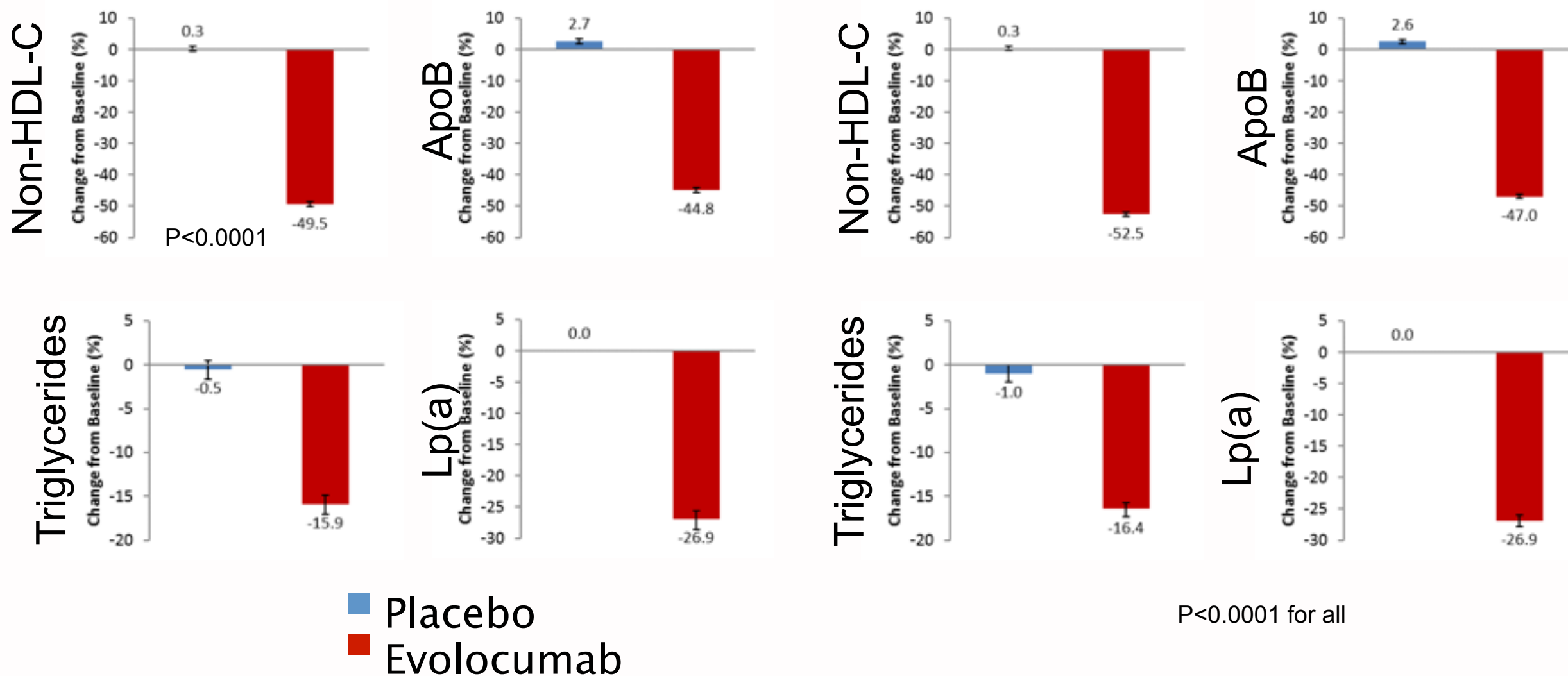
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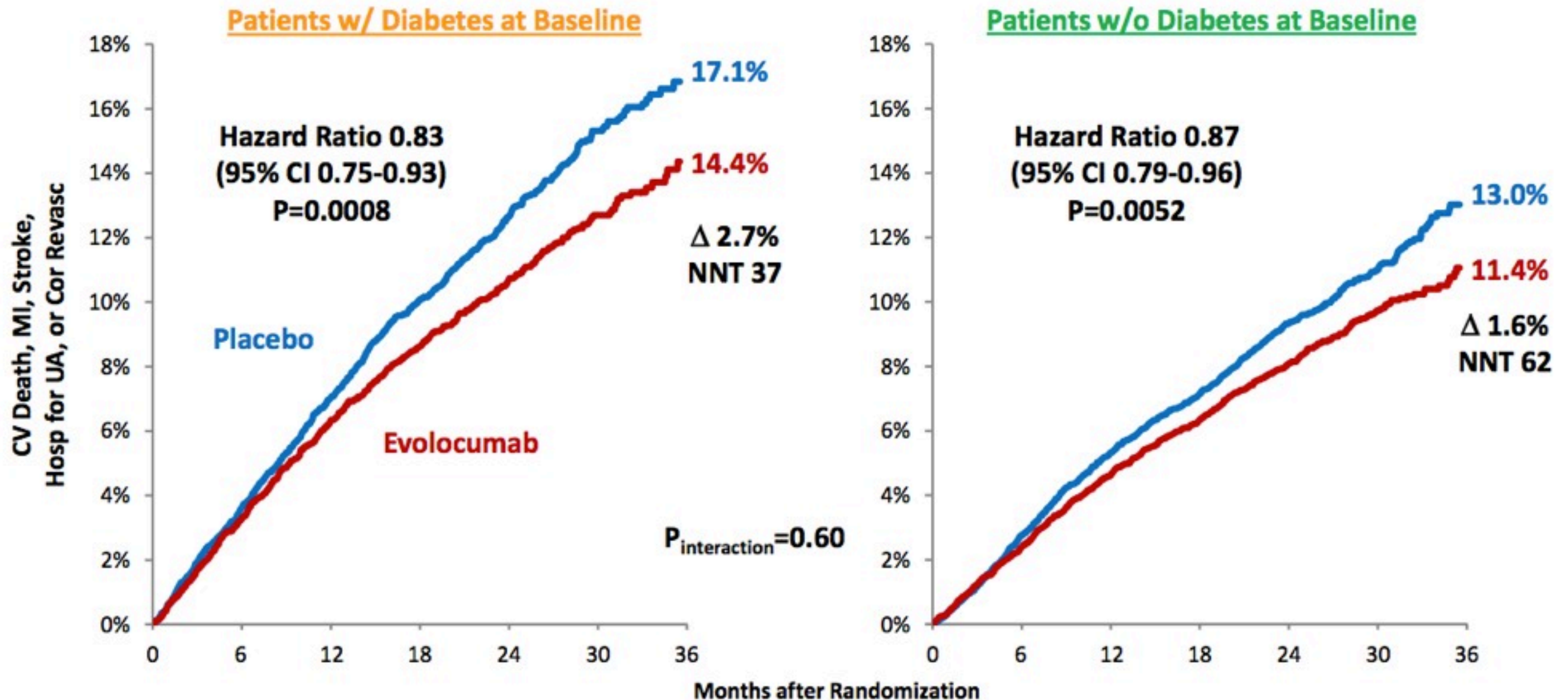
Patients w/o Diabetes at Baseline



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FOURIER diabetes substudy

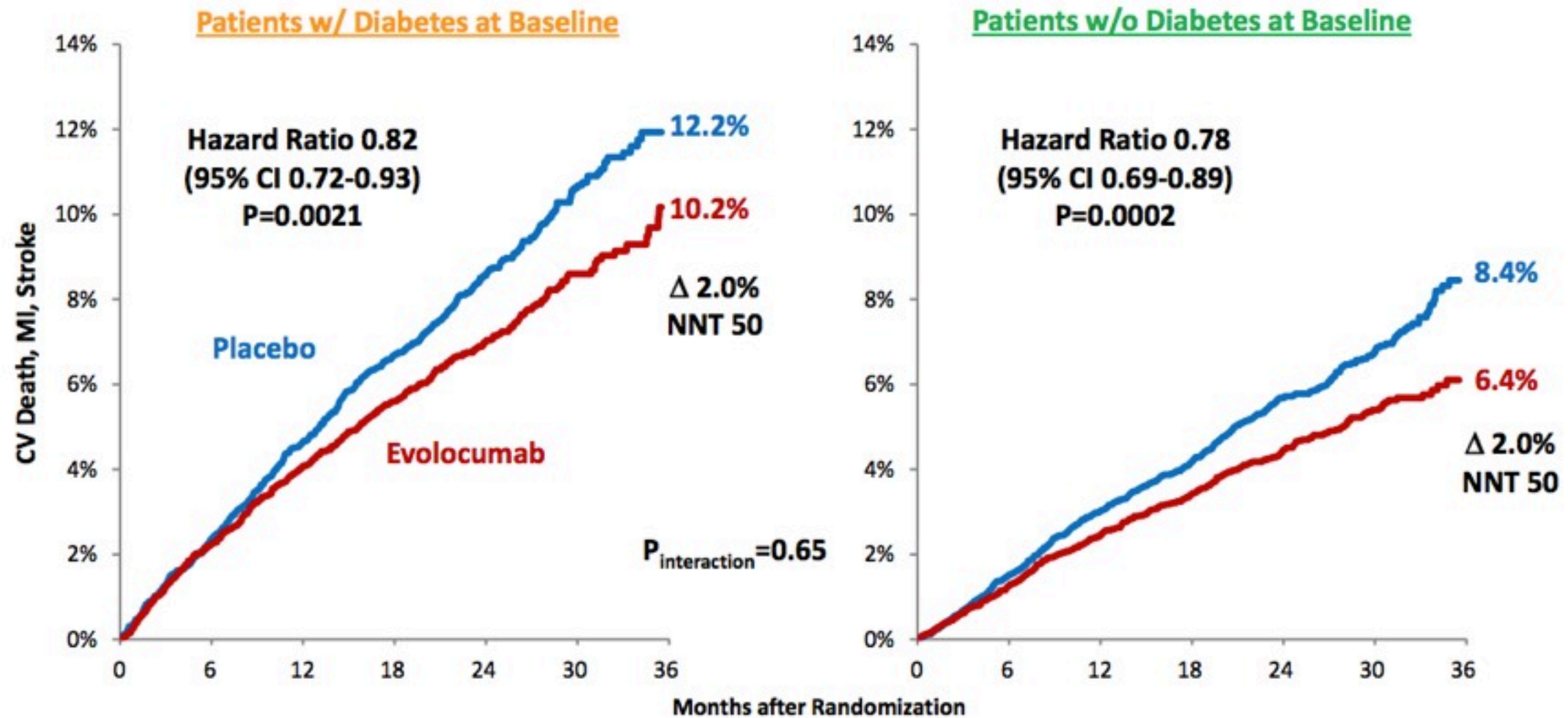
effect of evolocumab on primary endpoint



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effect of evolocumab on secondary endpoint



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FOURIER diabetes substudy

CV outcomes: no specific outlier

	Patients with Diabetes at Baseline			Patients without Diabetes at Baseline		
Endpoint	EvoMab (N=5515)	Placebo (N=5516)	HR (95% CI)	EvoMab (N=8269)	Placebo (N=8264)	HR (95% CI)
CVD, MI, stroke, UA, or revasc	14.4	17.1	0.83 (0.75-0.93)	11.4	13.0	0.87 (0.79-0.96)
CV death, MI, or stroke	10.2	12.2	0.82 (0.72-0.93)	6.4	8.4	0.78 (0.69-0.89)
Cardiovascular death	3.6	3.5	1.05 (0.83-1.34)	1.8	1.7	1.04 (0.80-1.35)
MI	5.5	7.5	0.77 (0.65-0.92)	3.7	5.5	0.69 (0.58-0.81)
Stroke	2.9	3.2	0.79 (0.62-1.01)	1.7	2.2	0.79 (0.60-1.03)
Hosp for Unstable Angina	2.3	2.4	0.93 (0.70-1.22)	2.2	2.3	1.04 (0.82-1.31)
Coronary revasc	7.4	10.0	0.77 (0.66-0.88)	6.8	8.6	0.79 (0.70-0.90)

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Conclusions

- Patients w/ diabetes at substantially higher risk of CV events
- Evolocumab efficacious in ASCVD patients w/ & w/o diabetes
 - 57-60% ↓ in LDL-C
 - 18-22% relative risk reductions in CVD/MI/stroke; benefit ↑ over time
 - Given higher baseline risk, larger absolute risk reduction in CV events with evolocumab in patients with diabetes (particularly coronary revasc)
- Evolocumab safe and well-tolerated
 - No increased risk of diabetes, even in patients with prediabetes
 - No worsening of glycemia